## REMARKS

The Final Office Action mailed October 23, 2008 has been carefully reviewed and the following remarks are made in response thereto. A Notice of Appeal was filed on January 22, 2009. This response is submitted with a Request for Continued Examination and a Petition for Extension of Time for three months, to and including June 22, 2009.

**Interview Summary**

Applicant's representative, Einar Stole, conducted a telephone interview with Examiner Emily M. Le on June 4, 2009 in which the Vande-Velde and Zanone references were discussed, along with the distinctions of the present invention over these references as will be discussed in detail *infra*. The Examiner indicated that the distinctions be submitted to her in a response with an RCE. Applicant appreciates the Examiner's time and consideration in granting an interview after a Final Rejection.

Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Claims 11-12, 17-67 are pending. As a result of restriction and elections, claims 17-20 and 32-66 have been withdrawn. By this amendment, claim 1 has been amended to remove non-elected subject matter. Previously withdrawn claims 17-20, 43-45, and 48-55, directed to non-elected subject matter, have been cancelled. Previously withdrawn method claim 32 has been amended to incorporate the limitations of product claim 1 and it is requested that claims 32 and dependent claims therefrom 33-42, 46-57, and 56-67 be rejoined and considered for allowance along with the product claims. New claim 68 has been added. Support for this claim can be found in the specification at paragraph [0041].

**I. Summary of the Office Action**

1. Claims **11-12, 21-42, 46-47,** and **56-68** will be pending upon entry of this amendment and response.

2. The Examiner rejected claims 11-12, 21-22, 30-31, and 67 under 35 U.S.C. 103(a) as being anticipated by Vande-Velde, U.S. PG Patent No. 20040013695, in view of Zanone *et al.*, U.S. Patent No. 6,497,859.

3. The Examiner rejected claims 23-25 under 35 U.S.C. 103(a) as allegedly being unpatentable over Vande-Velde and Zanone *et al.*, as applied to claims to claims 11-12 and 21-22, in view of Martin *et al.*, U.S. PG Patent No. 20030049271.

4. The Examiner rejected claims 23 and 26-29 under 35 U.S.C. 103(a) as allegedly being unpatentable over Vande-Velde and Zanone *et al.*, as applied to claims 11-12 and 21-22, in view of Kricek, *et al.*, U.S. Patent No. 6,610,297.

5. The Examiner rejected claims 11-12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7,348,010, in view of Vande-Velde and Zanone *et al.*

6. The Examiner provisionally rejected claims 11-16 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 63-64 of copending Application No. 10/490,920 in view of Vande-Velde and Zanone *et al.*

7. No claims were allowed.

## II. Response to the Office Action

### 1. Claim Rejection under § 103

The Examiner rejected claims 11-12, 21-22, 30-31, and 67 under 35 U.S.C. 103(a) as being anticipated by Vande-Velde, U.S. PG Patent No. 2004/0013695, in view of Zanone *et al.*, U.S. Patent No. 6,497,859. The Examiner contends that Vande-Velde teaches an oral vaccine composition comprising an antigenically active substance and an antacid for dissolution in the mouth. The Examiner acknowledges that it is not apparent whether the antacids disclosed in Vande-Velde act protectively through mucous membranes. However, the Examiner cites Zanone *et al.*, for the teaching that numerous compounds, including those taught by Vande-Velde and those mentioned in the present application, can be used as antacids. Therefore, the Examiner reasons that it would have been obvious to use an antacid disclosed by Zanone, which include

those of the present invention, with the composition of Vande-Velde, because the use of functional equivalents, *i.e.*, one antacid for another, is routinely practiced in the art.

Applicants respectfully traverse the rejection. As previously mentioned, the antacids described in Vande-Velde are limited to antacids that perform a neutralization reaction to reduce acidity in the stomach. Specifically Vande-Velde at paragraph [0006] states:

> In another aspect of the present invention the oral vaccine quick dissolving cake comprises an antacid. The antacid being such that when dissolved in saliva, and swallowed, it is capable of raising the pH of the stomach contents such that the vaccine antigen is not substantially degraded in the stomach. Most preferably the antacid is water insoluble and also acts as an adjuvant, in addition it is more preferred that when antigen is adsorbed to the surface of the insoluble antacid/adjuvant the antigen is protected from stomach acid.

See also, paragraph [0092]. Vande-Velde does not teach the currently recited class of antacids, namely antacids **that act protectively through the mucous membrane**. To the contrary, Vande-Velde discloses that the preferred antacids are the *gastric acid neutralizing antacids* such as organic acid carboxylate salts, such as a salt of citric acid, aluminum hydroxides or phosphates, magnesium hydroxide, and most preferably, calcium carbonate or aluminum hydroxide. See paragraphs [0033], [0034], and [0037] of Vande-Velde. These antacids are not mucosally protective antacids.

Antacids that act protectively through the mucous membrane, such as sucralfate and carbenoxolone (paragraph [0016], [0035]), are characterized by a different mode of action than those disclosed by Vande-Velde. For example, sucralfate is a locally-acting substance that, when in an acidic environment (pH <4), binds to hydrochloric acid of the stomach to form a cross-linking, viscous, paste-like material capable of acting as an antacid buffer that protects the mucosa from endogenous and exogenous noxious agents for as long as six to eight hours after a single dose. These cytoprotective properties result from a locally-formed layer that covers ulcers and erosions which inhibits the diffusion of protons and pepsin to the damaged mucosa.

Sucralfate also absorbs both peptide and bile acids, and prevents back diffusion of hydrogen atoms.

**Applicants note that in their previous response, it was stated that sucralfate has no effect on increasing gastric pH. This was an unintentional error, as the foregoing and specification specifically teach that sucralfate raises gastric pH. See paragraph [0012] and [0014] of the present specification (publication 2005/0226894).**

Accordingly, Vande-Velde does not teach antacids that act protectively through the mucous membrane.

Moreover, the antacids disclosed in Vande-Velde must be capable of dissolving in the oral cavity so that they can neutralize stomach acid when swallowed. See paragraphs [0006] and [0092] of Vande-Velde. One of skill in the art would not have been motivated from the teachings of Vande-Velde to use the elected species, sucralfate, because sucralfate is not dissolvable at neutral pH, *i.e.*, in saliva, as required by Vande-Velde. See Exhs. 1 and 2 to this response. Exhibit 1 is a Material and Safety Data Sheet for sucralfate which shows that sucralfate does not dissolve at neutral pH (in water) but dissolves in dilute hydrochloric acid (low pH-acidic) or sodium hydroxide (high pH-basic) (see p. 4). Exhibit 2 is an article by Eisenbrandt showing that the pH of saliva is between 6.69 and 6.75, *i.e.*, neutral pH.

Moreover, there is an unexpected increase of vaccine immunogenicity when using antacids that protectively act through the mucous membrane. The instantly claimed composition provides for a vaccine that generates an improved immune response involving the production of immunoglobulins. The response is a Type 2 immune response which involves the generation of IgE. See paragraphs [0006-0007]. Vande-Velde do not teach or suggest that antacids can be used to stimulate a Type 2 immune response. In fact, Vande-Velde teaches that the oral formulations comprising antacids disclosed therein actually elicit a **lower** immune response than corresponding intramuscular injections. See paragraph [0069] ("In general, the oral lyoc formulations elicited lower serum IgG responses than the OspA IM booster."). In contrast, the data in Figure 1 of the instant application shows an unexpectedly **higher** immunogenic response when using sucralfate, for example, as compared to a corresponding intramuscular injection

The Examiner points out that Vande-Velde teaches that the oral formulations that include the antacid $CaCO_3$ induce a "significant" response after two subsequent boosters. However, this is clearly inferior to the presently claimed vaccine, in which the immune response is improved

after a single, first administration (see Example 1, paragraph [0040]). The present specification also states that the presently claimed vaccine produces higher IgE values in comparison with $Al(OH)_3$ administered intraperitoneally. See paragraph [0041], and Group B versus Group C. Tellingly, Vande-Velde does not provide any specifics or quantitative results on the type of the immune response disclosed, so it is impossible to discern either the type or magnitude of the alleged "significant" immune response that occurs following the boosters.

The Examiner's citation to Zanone *et al.* to simply show that sucralfate is an antacid does not cure the deficiencies of Vande-Velde. Zanone does not provide the motivation to use a mucosally protective antacid, let alone in a vaccine. Zanone *et al.* is generally directed to the use of cooling agents for soothing inflammatory irritations of the upper gastric tract caused by acid reflux (gastric acid irritation). Zanone also teaches that antacids can be administered with the cooling agents to treat the underlying problem, *i.e.*, reduce the acid of gastric acid so it does not continue to irritate and burn the upper gastric tract. But the cooling agents do not treat the underlying condition, they just act as a palliative agent to give the patient the sensation of relief during the time it takes for the co-administered antacid to work. See col. 1, ll. 38-54 of Zanone, reproduced below:

> In pharmaceutical compositions, such as antacids, useful for treating upper gastrointestinal tract distress, such as heartburn, indigestion, stomachache and the like, cooling agents are generally employed as excipients to provide cooling sensation when the pharmaceutic composition is consumed. **Generally, the active pharmaceutical agent in pharmaceutical compositions for treating upper gastrointestinal tract distress will not immediately begin to relieve the condition causing the distress. Cooling agents, used in the pharmaceutical compositions as excipients, however, provide cooling sensation to the mouth, throat and gastrointestinal tract so that the pharmaceutical composition will be perceived by the consumer as acting faster to alleviate the gastrointestinal distress.** Thus, the consumer is provided with the sensation of relief although the active principle of the pharmaceutical composition has not begun to alleviate the conditions causing the distress.

(emphasis added).

However, nowhere do Zanone *et al.* teach or suggest that the use of antacids that are mucosally protective. The antacids mentioned in Zanone include "antacid agents," which include the aluminum, calcium and magnesium salts that neutralize stomach acid, and "acid secretion prevention agents," such as the $H_2$ receptor blocking agents, which include cimetidine, famotidine, ranitidine and omeprazole. See col. 5, ll. 28-54. Sucralfate is disclosed among a group of antacids designated "antacid agents." In fact, Zanone does not disclose any mucosally protective agent as presently claimed. While the cooling agent soothes the upper GI tract, it is not a treatment (see above quote). Further, the cooling agents do not bind to hydrochloric acid of the stomach to form a cross-linking, viscous, paste-like material capable of acting as an antacid buffer that protects the mucosa from endogenous and exogenous noxious agents, and is therefore not "mucosally protective" as presently claimed.

Lastly, Zanone does not mention that the antacids, alone or in combination with the cooling agents can be used to induce or increase an immune response.

Viewing the prior art as a whole, a person of ordinary skill in the art would not have been motivated to combine the teachings of Vande-Velde and Zanone *et al.* The only disclosure that of using a mucosally-protective antacid in a vaccine comes from the present specification. The only disclosure that sucralfate is a mucosally protective antacid comes from the present specification. Neither reference discloses the desirability of using a **mucosally protective antacid**, and neither reference, alone or in combination, provides the motivation or other reason for a skilled artisan to specifically select **a mucosally protective antacid** for use in an oral vaccine. Thus, the Examiner has improperly used hindsight, or the teachings of the application under examination, to improperly combine Vande-Velde and Zanone.

An additional reason why one of ordinary skill in the art would not have been motivated to select a mucosally-protective antacid from among the list disclosed in Zanone is because Vande-Velde specifcially discloses that the preferred antacids for use are the *gastric acid neutralizing antacids*. See paragraphs [0033], [0034], and [0037] of Vande-Velde. These antacids are not mucosally protective antacids.

The above, taken together with the additional fact that the use of sucralfate does not appear to dissolve at neutral pH, and therefore would not dissolve in saliva as required by

Vande-Velde, is compelling evidence against combining sucralfate disclosed in Zanone for use in the vaccine of Vande-Velde. Thus, even assuming *arguendo* that one would have been motivated to select an antacid from among those dissolved in Zanone to use with the oral vaccine of Vande-Velde, one would certainly not select sucralfate.

Lastly, Vande-Velde teaches that the combination of an oral vaccine comprising an antigen and an antacid does not lead to an improved immune response following a *single* administration, but only after boosters. See paragraph [0069] of Vande-Velde. Vande-Velde also teaches the particularly preferable use of aluminum hydroxide as the antacid, which is one that is shown in the instant specification to be inferior to the antacid used in the presently claimed vaccine. See paragraph [0041] of the instant specification.

Accordingly, a person of ordinary skill in the art would not have been motivated to use a mucosally protective antacid from the teachings of Vande-Velde and Zanone, let alone have a reasonable expectation of success to combine these references and arrive at the claimed vaccine.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

The Examiner rejected claims 23-25 under 35 U.S.C. 103(a) as allegedly being unpatentable over Vande-Velde and Zanone *et al.*, as applied to claims to claims 11-12 and 21-22, in view of Martin *et al.*, U.S. PG Patent No. 20030049271. The Examiner also rejected claims 23 and 26-29 under 35 U.S.C. 103(a) as allegedly being unpatentable over Vande-Velde and Zanone *et al.*, as applied to claims 11-12 and 21-22, in view of Kricek, *et al.*, U.S. Patent No. 6,610,297.

Applicants respectfully traverse these rejections. Neither Martin *et al.* nor Kricek *et al.* remedy the insufficiency of the Examiner's primary obviousness rejection over Vande-Velde and Zanone. Martin *et al.* is generally directed to *Streptococcus* antigens conjugated to carriers and do not teach or suggest the use of mucosally protective antacids as adjuvants, or an increased immune response when using the same. Similarly, Kricek *et al.* discloses antigen mimotopes conjugated to carriers and do not teach the use of mucosally protective antacids as adjuvants, or an increased immune response when using the same. For these reasons, withdrawal of these rejections under 35 U.S.C. § 103(a) is respectfully requested.

**2. Double Patenting**

The Examiner rejected claims 11-12 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7,348,010, in view of Vande-Velde and Zanone *et al.* The Examiner also provisionally rejected claims 11-16 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 63-64 of co-pending Application No. 10/490,920 in view of Vande-Velde and Zanone *et al.* Applicants respectfully traverse these rejections.

As discussed above, a person of ordinary skill would not have a reasonable expectation of success of an improved immune response using the claimed antacid species. Neither U.S. Patent No. 7,348,010 nor U.S. Application No. 10/490,920 cure the deficiency of the Examiner's initial obviousness rejection the use of the claimed class of mucosally protective antacid, or an increased immune response when using the same. In contrast, Vande-Velde teaches away from the use of the claimed antacids. For these reasons, withdrawal of these rejections under non-statutory obviousness-type double patenting is respectfully requested.

## III. Conclusion

Applicant believes that the above-referenced application is in condition for allowance. Reconsideration and withdrawal of the outstanding rejections, rejoinder of the withdrawn method claims, and early notice of allowance to that effect is respectfully requested.

**EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 13-3250, reference No. 37488.00400. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

If the Examiner finds that a telephone conference would further prosecution of this application, the Examiner is invited to contact the undersigned at 202-835-7589.

Respectfully submitted,

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